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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
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SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
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MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
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- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

(88) Date of publication of the international search report:
26 February 2004

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: FORMULATION STRATEGIES IN STABILIZING PEPTIDES IN ORGANIC SOLVENTS AND IN DRIED STATES

(57) Abstract: The invention relates to stabilized formulations of therapeutically active peptides, particularly PACAP 66. Formulations of the invention include a peptide containing at least one histidine residue, a transition metal salt and an organic solvent. The above formulations may contain peptides that have at least one asparagine residue and are acidified and dried (such as spray-dried or freeze-dried) before formulation preparation. Other formulations of the invention relate to stabilized formulations of PACAP 66 or peptides containing an asparagine residue, which are acidified and dried (such as spray-dried or freeze-dried) with or without a transition metal salt.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|--|---|
| Applicant's or agent's file reference MSB-7293 PCT | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/US03/04790 | International filing date (day/month/year) 14 FEBRUARY 2003 | (Earliest) Priority Date (day/month/year) 14 FEBRUARY 2002 |
| Applicant BAYER PHARMACEUTICAL CORPORATION | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/04790

| A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 38/16, 38/00, 38/24; C07K 1/00 US CL : 514/6, 12; 530/324, 399, 400, 402; 930/170 According to International Patent Classification (IPC) or to both national classification and IPC | | |
|---|---|--|
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/6, 12; 530/324, 399, 400, 402; 930/170 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Extra Sheet. | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | WO 01/23420 A2 (BAYER CORPORATION) 05 April 2001, entire document. | 1-65 |
| Y | US 5,376,637 A (SAWAI et al) 27 December 1994, entire document. | 1-65 |
| Y | US 5,234,907 A (BOLIN) 10 August 1993, cols. 3-9 and SEQ ID NOS: 1-93. | 1-65 |
| X | US 5,830,998 A (MACCECCHINI) 03 November 1998, col. 3, lines 30-60; col. 12, lines 18-24; col. 16, lines 1-21 and Figure 1. | 1-2, 5-9, 34-36, 38-39 and 41-43 |
| X | YANG et al. Examining the zinc site of the amyloid- β peptide. Eur. J. Biochem. 2000, Vol. 267, pages 6692-6698, especially pages 6692-6693 and 6697. | 1, 6-7, 34-35, 42-43, 54, 58-59 and 60 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex. | | |
| * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family | | |
| Date of the actual completion of the international search 29 JUNE 2003 | | Date of mailing of the international search report 17 JUL 2003 |
| Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3280 | | Authorized officer ABDEL A. MOHAMED Telephone No. (703) 308-0196 |

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, MEDLINE, EMBASE, BIOSIS, WPIDS

search terms: hormone or pituitary adenylate cyclase activity polypeptide or PACAP or PACAP66, or vasoactive intestinal polypeptide or VIP, divalent or metal or zinc or copper or iron or manganese or nickel or cobalt, formulat? or pharmaceut? or composit?, stabiliz?, organic solvent, acid, HCL or TFA, lyophiliz? or freeze-dry? or spray-dry?